CLINICAL INVESTIGATION

CGRP antagonists for the treatment of migraine: rationale and clinical data

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CGRP is localized in primary spinal afferent C and Aδ fibers of the sensory ganglia and in the CNS, for example, in the colliculi and cerebellum. Trigeminal nerve activation results in antidromic release of CGRP that leads to vasodilatation via a CGRP-receptor complex (calcitonin-like receptor and RAMP1). At central synapses in the trigeminal nucleus caudalis, CGRP on second-order neurons transmits pain signals centrally. Calcitonin-like receptor and RAMP1 are widely expressed throughout the brain and in intracranial arteries and the trigeminal system. CGRP does not induce neurogenic inflammation or sensitization at peripheral meningeal sites, but relays nociceptive information to the second-order neurons in the brainstem. Recently developed CGRP-receptor antagonists have excellent antimigraine effects and a low side-effect profile. The CGRP-receptor antagonists reduce signaling in the trigeminovascular pathway at multiple sites and at central sites, however, the exact site of antimigraine effect is still under debate.

Keywords: CGRP • CGRP receptor antagonists • migraine • telcagepant • trigeminovascular reflex

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Primary head-pain syndromes such as migraine and cluster headache are common types of chronic recurring head pain that are clinically well defined. The vasomotor response of the sensory nerves in the peripheral circulation has a counterpart in the cerebral circulation with the trigeminal system. The pain-sensitive supratentorial structures are innervated by sensory nerve fibers arising from pseudounipolar neurons with their cell bodies in the first division (ophthalmic branch) of the trigeminal ganglion (TG), which connect to the CNS at second-order sensory neurons within the brain stem trigeminal nucleus caudalis (TNC) and at C_{1-2} [1]. Antidromic or local mechanical stimulation of sensory nerve endings causes dilatation of intracranial vessels via the release of CGRP from the trigeminovascular system in humans [2,3]. Moreover, release of CGRP from perivascular nerves in the meninges (dura mater) and in the cerebral circulation [2,4–6] is associated with migraine pain. Recent advances in our understanding of CGRP mechanisms, central pain processing and biology suggest that the pathophysiology of migraine is far more complex and that vascular activation may be just one of many factors involved in the migraine pathogenesis.

Basic facts on CGRP

■ Expression of CGRP

CGRP is a 37 amino acid neuropeptide, identified three decades ago [7]. The calcitonin gene was unexpectedly found to encode two different mRNAs and either calcitonin or αCGRP mRNA is expressed, depending on anatomical localization. αCGRP is the predominant expression product in the nervous system. A second CGRP gene has been discovered that forms βCGRP, and it is primarily

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expressed in the enteric sensory system in the gut and inner organs [8].

CGRP is widely expressed in both the central and peripheral nervous systems. In the CNS, CGRP-containing cell bodies have been found in a number of areas associated with migraine pathophysiology such as hypothalamus (trigger), superior colliculi (visual symptoms), inferior colliculi (phonophobia), brainstem and trigeminal complex (head pain, nausea) and cerebellum [9]. Specifically, these areas include the medial preoptic nucleus, the preoptic area, the anterior hypothalamic nuclei, the periventricular nucleus, the perifornical area, the lateral hypothalamus/medial forebrain bundle area, the premamillary nucleus, the medial amygdaloid nucleus, the ventromedial nucleus of the thalamus, the hippocampus and the dentate gyrus, the periventricular gray and the area around the fasciculus retroflexus (parafascicular area), extending laterally over the lemniscus medialis [10,11]. In the mesencephalon, CGRP-positive cells are found in the peripeduncular area ventral to the medial geniculate body, extending dorsally along its medial aspects. Positive CGRP-containing cell bodies also are seen in the paratrigeminal nucleus as well as in the superior colliculus. Peptidergic fibers containing CGRP have been found to innervate the anterior pituitary of the human [12]. The distribution of CGRP in the CNS in extensive receptor binding studies have shown large mismatches [13]. These anatomical studies suggested roles of CGRP in synaptic and metabolic regulation and as part of components in the central somatosensory system. In the hippocampus it may serve a role as a modulator of CNS injury/immune response [14]. Changes in CGRP binding may be altered in stress-related situations [15]. Interestingly, there is high expression of CGRP in the cerebellum and inferior olivary complex suggesting that it may play an important modulatory role in modulating pain transmission in the brainstem [16].

General functions of CGRP

Centrally, evidence is emerging that CGRP may play an important autocrine and paracrine function in many areas. Activation of CGRP receptors on cultured TG neurons increased endogenous CGRP mRNA levels and promoter activity [17]. CGRP has also been shown to differentially regulate cytokine secretion from cultured TG glia [18]. Although CGRP has a number of effects, its most pronounced action is that of intracranial vasodilatation and in transmission of nociception [19].

The best-known function of CGRP is its effect on peripheral vasculature. It acts on smooth muscle cells and causes vasodilatation via a nonendothelial mechanism through activation of adenylyl cyclase [20]. The release of perivascular peptides relax cerebral arteries concomitant with stimulation of cyclic adenosine monophosphate accumulation or release of an endothelium-derived relaxing factor in the cat [21]. The trigeminal nerve fibers mediate dilatation of brain vessels, increases in cerebral blood flow [22,23] and have an important role in the trigeminovascular reflex [24,25].

There is a dense supply of thin CGRP-containing nerve fibers in intracranial vessels and these originate in the TG [24,26]; first discovered in 1984 [27]. The CGRP-positive perivascular nerve fibers in intracranial vessels (dural as well as cerebral) originate in the first division of the TG while the other branches of the fifth cranial nerve supply other parts of the head with sensory innervation. There is significantly more CGRP immunoreactivity than that of substance P; however, these peptides colocalize in the perivascular nerves. Electrical field stimulation or capsaicin treatment [25,28] causes local vasodilatation and release of CGRP from the perivascular nerve fiber endings. These effects are attenuated by administration of a CGRP receptor blocker acting postsynaptically [4–6,29,30] or a triptan acting at presynaptic sites to suppress release [4,31] and as a vasoconstrictor of human intracranial arteries [32].

The CGRP-containing nerve cell bodies constitute more than 40% of the neurons in the TG; they have functional connections with neurons in the TNC and in related extensions down to the C_{1-2} level on one hand and the perivascular nerve fiber network of intracranial vessels on the other [22,23]. Early horseradish peroxidase tracing studies showed anatomical connections between meningeal (dural) vessels and the TG [33]. Subsequent retrograde tracing with True Blue in combination with neuropeptide immunocytochemistry revealed that the sensory fibers and the trigeminal neurons colocalize CGRP and substance P [34,35], while denervation (trigeminal nerve lesion) abolished these neuropeptides from the perivascular nerves [26]. Recent retrograde tracing from intra- and extracranial arteries, and the superior sagittal sinus have shown that the perivascular sensory C-fibers terminate in lamina I/II and the mechanoceptor Aδ-fibers in lamina III/IV of the brain stem [36–38]. The tracing studies furthermore suggest a somatotopic organization of the perivascular nerve fiber projections in the brain stem. The trigeminovascular system [24,25] has a primary involvement in cranial sensory functions, but also acts as a vasodilator pathway with antidromic release of CGRP, putatively as a response to localized cerebrovascular constriction. In the brain stem it is primarily the C-fibers that contain CGRP and these connect in layers I/II with secondary neurons that have postjunctional CGRP receptors. Work by Lennerz *et al.* suggested that the CGRP receptors are situated presynaptically on primary afferent endings to regulate nociceptive transmission and thereby modify signals to the CNS [39]. Recent work by Eftekhari and Edvinsson [40] using a set of novel developed antibodies towards calcitonin-like receptor (CLR) and RAMP1 suggests that C-fibers storing CGRP and Aδ-fibers storing CLR/RAMP1 both end up in lamina I/II in the C1–2 level and the TNC. This indicates interaction between the two nerve fibers at the brain stem level but this is a postsynaptic interaction.

Role of CGRP in migraine pathophysiology

The potential role of CGRP in migraine pathophysiology was first suggested in 1984 [27] and a growing body of evidence suggests a pivotal role for CGRP in the pathogenesis of primary headaches [22,23]. In spontaneous migraine attacks there is significant release of CGRP but not of any other neuropeptide [22,41,42]. The role of the sensory nerves located around the intracranial vessels has been analyzed in humans in conjunction with stimulation of the TG; this resulted in unilateral blood flow increases, release of CGRP and substance P and in ipsilateral facial flushing [22,23]. In addition, glycerol injection into the TG-induced a slight increase in human cerebral blood flow (CBF) [43] while cutaneous stimulation in trigeminal neuralgia resulted in facial flushing and associated CGRP release [44]. These studies strongly suggest that there is release of CGRP from the trigeminovascular system during activation of the TG.

Current theory proposes that migraine is a disease with a genetic predisposition. Anttila *et al.* [45] reported an association in a genome-wide association study of migraine, which suggests a site that regulates the expression of the primary glutamate transporter in the brain, EAAT2/GLT-1. For hemiplegic migraine there are data to suggest that alterations in ion channel genes render CNS neurons unstable and capable of initiating a migraine attack [46,47]. The current view of migraine pathophysiology furthermore suggests that the trigeminal system is an essential part of the disease expression. Hypothetically, the mechanisms involve activation of the trigeminovascular reflex as a defense mechanism towards cerebrovascular constriction elicited either due to spreading depression [48–51] or other localized cerebrovascular vasomotion [52]. The cerebral circulation requires high and constant flow and metabolism. Hypothetically, cerebral vasoconstriction is sensed by the trigeminal sensory nerve fibers with a subsequent antidromic release of CGRP to maintain local brain blood flow within normal limits. This view is supported by studies of patients that have suffered a subarachnoid hemorrhage. Their cerebrovascular levels of CGRP were deplete and the administration of CGRP could reverse the vasospasm [53,54]. The trigeminal activation results in orthodromic activation of neurons in the TNC with subsequent second-order neuron involvement and mediation of the central aspects of pain within the two regions of termination; sensory C-fibers in lamina I/II and Aδ-mechanoreceptor fibers in lamina III–IV [55].

The results from TG stimulation in trigeminal neuralgia patients led us to investigate neuropeptides associated with the autonomic and sensory nerves during migraine attacks [22]. The concentration of neuropeptide Y (NPY; marker for sympathetic nerves), vasoactive intestinal peptide (VIP; parasympathetic activity), and CGRP and substance P (markers for sensory nerves) were analyzed in the cranial venous outflow. There were no changes in the levels of NPY, VIP or substance P during migraine attacks. However, a marked increase in CGRP levels were observed in patients during attacks of migraine with aura or without aura [42]. The release of CGRP rather than substance P is possibly due to the fact that the intracranial circulation is preferentially innervated by CGRP-containing sensory fibers from the TG [3,34] and it is supported by the fact that there is no antimigraine effect of substance P receptor antagonists.

In the clinical setting nitroglycerine is used to elicit migraine-like attacks [56]. Further experiments using this model have provided supportive data demonstrating a linear correlation between the increased levels of CGRP and the intensity of the headache [57,58]. It is worth noting that low pain results in no significant increase in venous CGRP, an observation supported by Juhaz *et al.* [58] and Kruuse *et al.* [59]. In addition, Fanciullacci *et al.* [60] observed that nitroglycerine did not elicit cluster headache attacks if the patient was not in a 'prone status'. Hence the disease was active and a small stimulation could then elicit the full cluster headache attack. Studies of the perfused middle cerebral artery (MCA) [4,57,61] showed that CGRP does not readily pass the blood–brain barrier (BBB), which agrees well with this supposition. The nerve fibers are situated in the adventitia and act on the receptors located in the smooth muscle cells. Thus, a low degree of perivascular CGRP release likely occurs in mild–moderate attacks but it is necessary to have a large release to measure the peptide in the cranial venous effluent. Any negative data would fall into this category [62]. We have discussed this matter in detail. Our view is that it is due to a methodological error that the Copenhagen group could not confirm what other

groups in different countries have reported [63]. This view is supported by human studies of subarachnoid hemorrhage where the CGRP increase in the cranial venous outflow and in the cerebrospinal fluid (CSF) correlated with the degree of vasoconstriction measure with transcranial Doppler [53,54]. In addition, following sumatriptan or rizatriptan administration, the plasma levels of CGRP returned to control with successful amelioration of the headache [4,57,61]. These results have been confirmed in experimental studies using zolmitriptan, rizatriptan, sumatriptan and dihydroergotamine. The 5-$HT_{1B/1D}$ receptors are expressed on human TG cells and on trigeminal sensory fibers [64], thus providing sites for presynaptic inhibition of the CGRP release and of contractile 5-HT_{1B} receptors in intracranial arteries [32]. However, there is still the question if the vasomotor effect of the triptans is of pivotal importance for the antimigraine effect.

CGRP receptors

Early pharmacological studies focused on the use of CGRP agonists and the CGRP fragment $CGRP_{8-37}$ to discriminate between CGRP receptor subtypes [19].

Human and rat CLR have been cloned; CLR is a seven-transmembrane domain G-protein-coupled receptor, which shares 55% sequence identity with the calcitonin receptor [65]. Functional CGRP and adrenomedullin (AM) receptors are derived from CLR and the phenotype is determined by co-expression with a RAMP. Co-expression of CLR with RAMP1 results in $CGRP_1$ receptor pharmacology, while co-expression with RAMP2 or RAMP3 yields an AM receptor or possibly a combined receptor (CGRP and AM). We have performed immunohistochemistry and did not find any AM but found some amylin in the TG [66]. However, the responses to amylin and AM have been disappointingly small [67], hence our view on the importance of these peptides in the trigeminovascular system is regarded as minor. Apart from contributing to the receptor specificity, the RAMPs enable expression of CLR on the cell surface [68]. Interestingly, the CGRP receptor requires another accessory protein for proper biological function, the RCP. RCP does not function as a molecular chaperone, but is involved in coupling of the receptor to downstream signaling pathways, such as adenylatecyclase activity.

CGRP receptors have classically been subdivided into two classes, $CGRP_1$ and $CGRP_2$, but the recent classification suggests that there exist only one CGRP receptor [69]. To address the question of where the CGRP receptors are localized in the trigeminovascular system immunocytochemistry has been performed. In intracranial blood vessels the CGRP receptor components were found in the smooth muscle cells [70]. In addition, we have observed both CLR and RAMP1 in human TG cells [71]. While CGRP can be easily seen in thin sensory fibers in the layers I/II of the TNC region, it has been difficult to obtain positive staining of the CGRP receptor components in this region; current data would suggest presynaptic and postsynaptic CGRP receptors in this region [72].

The basic mechanisms of vascular headaches presumably involve the presence of CGRP receptor components in cerebral and middle meningeal arteries (MMA) [70]. A recent study with MR angiography imaging provides data in humans for a vascular factor in attacks of migraine without aura [73]. The attacks were associated with dilatation of extra- and intracerebral arteries, and the headache located in relation to the dilatation. This agrees with our previous results that human cerebral (MCA) middle MMA and brain microvessels express mRNA for CLR, RAMPs1–3 and RCP [70]. Cultured smooth muscle cells and brain microvascular endothelial cells express mRNA for all components, except for RAMP3 [70]. The mRNA for the entire CGRP receptor is expressed on human intracranial arteries. Functional CGRP receptors are localized on the vascular smooth muscle cells of the cranial arteries in particular since the responses of cerebral veins to CGRP are very weak [24,74]. Pharmacological studies of cerebral arteries and MMA revealed that CGRP receptors dominate by inducing stronger dilatation of cerebral arteries than of the MMA, while the responses to amylin and AM are minor and mediated by the CGRP receptor. The CGRP-induced relaxation in humans is endothelium independent and occurs in parallel with activation of adenylyl cyclase. In addition, CGRP receptor mRNA, mRNAs encoding CLR and all three RAMPs have been observed in the smooth muscle cells of human cranial arteries [70,75,76]; however, it is RAMP1 that determines the functional phenotype. The results of Asghar *et al.* [73] support the involvement of the trigeminovascular system in migraine pain and its association with vasodilatation in regions related to the pain. This is thus, as the authors point out, an integral mechanism involved in migraine pathophysiology.

CGRP receptor antagonism

Based on the role of CGRP in migraine and the use of a nonvasoconstrictor in the treatment resulted in the proposal for CGRP receptor antagonism as a potential therapeutic target [22]. However, the antagonistic effect of $CGRP_{8-37}$ *in vitro* and *in vivo*, revealed that this antagonist has a short half-life and cannot be absorbed orally. A breakthrough in the CGRP field came with the development of a series of small molecule, potent CGRP receptor antagonists [77] and some molecular modifications of this compound [78].

The most potent of these, olcegepant demonstrates extremely high affinity for the human CGRP receptors with a pA_2 value in the pM range [79,80]. Interestingly, the antagonist is three log units more potent in human tissues as compared with that seen in experimental animals. The reason for this was revealed by Mallee *et al.* [81]; the high affinity of olcegepant was dictated strictly by hRAMP1. The region between amino acids 66–112 is critical for determining the pharmacology of these small molecule antagonists. The exact molecular mechanism by which RAMP1 modulates antagonist binding sites resides in an exchange of one nucleotide in RAMP1 [81].

A major advantage of a CGRP receptor blocker is the lack of vasoconstrictor ability; however, blocking the receptor of a strong vasodilator involves a theoretical risk of causing both peripheral and cerebral vasoconstriction [82]. In experimental studies, denervation or CGRP receptor antagonism did not change resting cerebral blood flow or metabolism, cerebral autoregulation or responses to changes in blood gases [4,83]. Olcegepant did not change the diameter of the superficial temporal or the MCA, or altered regional and global cerebral blood flow [84,85]. It was concluded that olcegepant does not affect the resting tone in the majority of investigated vessels, which gives olcegepant an advantage compared with other antimigraine compounds, such as triptans and ergot derivates. The site of the action of the antagonist is still not clear. With a closed cranial window model [30] olcegepant was found to inhibit dilatation of dural (meningeal) arteries after systemic CGRP (intravenously) and neuronal CGRP from perivascular nerves following transcranial electrical stimulation. These findings are in accordance with previous studies, since olcegepant inhibits CGRP-induced hypotension and TG-stimulated increase in facial blood flow in experimental studies [77]. By contrast, the antagonist did not significantly inhibit changes in the tone of cerebral arterioles or of local cortical cerebral blood flow [30]. This indicates that the effect of the compound is mainly extracerebral and that the antagonist does not readily pass the BBB, which correlates with the results from a clinical study [85]. There is recent support for this view. Perfusion of the isolated MCA showed that neither CGRP nor olcegepant passed the BBB to a major degree [67]. In healthy volunteers the CGRP antagonist prevented CGRP-induced headache and associated CGRP symptoms (flushing and sensation of heat). The increase in MCA diameter was small and not blocked by olcegepant; it is suggested that this is probably due to the reduction in blood pressure with a compensatory autoregulatory dilatation of the MCA. By contrast, the CGRP-induced effect was more pronounced in the superficial temporal and radial arteries and blocked by the CGRP antagonist [85].

Telcagepant (MK-0974) is a potent, selective antagonist of the human CGRP receptors but displays >1500-fold lower affinity for the canine and rat receptors as determined via [^{125}I]-human CGRP competition binding assays [86]. Telcagepant potently blocked α-CGRP-stimulated cAMP responses in human CGRP receptor-expressing HEK293 cells with an IC_{50} of 2.2 ± 0.29 nM. The unbound fraction in plasma was 4.1% in human plasma. In human cerebral and middle MMA *in vitro* assay, telcagepant showed a pA_2 value of 8.83 and 8.03 (~1 and 10 nM), respectively, in blocking α-CGRP-induced vasodilatation [87].

There is an ongoing debate [88,89] as to whether the origin of migraine pain is in the CNS, in perivascular nerves around the cranial arteries or both. Genetic studies have further added to this by pointing at genes involved in signaling in central neurons [45]. Functional studies of vascular innervations, vasomotor reactivity and receptor distribution of migraine patients and controls have not given evidence for a difference in expression.

There seems to be some consensus: 'although the onset of migraine attacks might take place in deep-brain structures, some evidence indicates that the headache phase depends on nociceptive input from perivascular sensory nerve terminals' [89]. It might be asked if the excitation or stimulation of dural and cerebral arteries elicits painful impulses. The original human work by Ray and Wolff showed that the direct stimulation of dural and major brain vessels elicited refereed pain localized extracranially [1]. The stimulation elicits local activation of sensory nerve fibers that go via the TG to different lamina in the brainstem at spinal TNC and C1–3 [90]. The CGRP-containing C-fibers exclusively end in lamina I/II where they contact second-order neurons to transmit signaling to higher centers in the CNS [90]. It is likely that the signaling can be modified by pathways of descending inhibition or facilitation in the brainstem, the thalamus and the cerebral cortex [91]. All these regions are potential sites for the antimigraine effects of CGRP antagonists [9].

Clinical studies on CGRP receptor antagonists for migraine

Olcegepant

The ability of CGRP receptor antagonists to treat acute migraine attacks was initially established with olcegepant (BIBN 4096 BS). In a proof-of-concept study, intravenously administered olcegepant was effective in relieving acute migraine pain and associated symptoms and was well tolerated with no cardiovascular or

Table 1. Efficacy of BIBN 4096 BS (olcegepant) in a clinical trial.

Drug and dose	Headache free at 2 h (n [%])	Headache relief at 2 h (n [%])
Olcegepant 0.25 mg iv. (n = 1)	0	0
Olcegepant 0.5 mg iv. (n = 4)	0	1 (25)
Olcegepant 1 mg iv. (n = 20)	4 (20)	9 (45)
Olcegepant 2.5 mg iv. (n = 32)	14 (44)	21 (66)*
Olcegepant 5 mg iv. (n = 16)	4 (25)	12 (75)
Olcegepant 10 mg iv. (n = 12)	3 (25)	8 (67)
Placebo (n = 41)	1 (2)	11 (27)

Data are number of patients fulfilling end point (n) with proportion (%) of patients with within parenthesis.
*p = 0.001 versus placebo.
iv.: Intravenous.
Data taken from [92].

cerebrovascular effects (Table 1) [92]. The results with olcegepant were encouraging, but migraine treatments are primarily administered on an outpatient basis and it is therefore important to develop CGRP receptor antagonists that can be taken orally or via another route, avoiding the need for patients to inject themselves.

Telcagepant

Telcagepant (MK-0974) was the first orally available CGRP receptor antagonist to pass Phase III trials for treatment of acute migraine. In clinical pharmacology studies, telcagepant was rapidly absorbed with a time to maximum concentration of approximately 1.5 h [93]. The terminal half-life was approximately 6 h. A greater than dose-proportional increase was observed in the area under the plasma concentration versus time curve from zero to infinity [94]. Following twice-daily dosing, with each dose separated by 2 h, steady state was achieved in approximately 3 to 4 days [94]. There were no clinically meaningful pharmacokinetic (PK) differences when compared across age and gender [94]. The PKs were not effected by migraine associated gastric stasis [95]. No consistent clinically relevant effects on ECG parameters, blood pressure or heart rate were observed in single- and multiple-dose clinical pharmacology studies [94]. Furthermore, an interaction study showed that telcagepant alone does not elevate mean arterial blood pressure (MAP) and co-administration of telcagepant with sumatriptan results in elevations in MAP similar to that following administration of sumatriptan alone in migraineurs during the interictal period [96].

The effectiveness of telcagepant in treating acute migraine was tested in a Phase IIb dose-finding study in which doses from 25 to 600 mg were explored [97]. Telcagepant 300 to 600 mg were shown to be effective in treating both acute migraine pain and migraine associated symptoms (Table 2). The efficacy and safety profiles of telcagepant were confirmed subsequently in three additional large pivotal Phase III acute efficacy migraine trials involving a total of 3293 telcagepant-treated patients [98–100]. All three trials demonstrated that both telcagepant 300-mg capsule/280-mg tablet and 150-mg capsule/140-mg tablet (300- and 150-mg capsules are bioequivalent to 280- and 140-mg tablets, respectively) are effective in treating migraine headache (2 h headache relief, 2 h headache freedom and 2–24 h sustained pain freedom; Table 2) and migraine associated symptoms (photophobia, phonophobia and nausea; Table 2). The multiple attack study showed that telcagepant 140 and 280 mg have consistent responses in treating migraine pain across 4 attacks (measured by the proportions of patients who had 2 h pain freedom/relief in at least three out of four attacks)[99].

Tolerability of telcagepant

Telcagepant was well tolerated with an adverse event (AE) rate similar to that of placebo (Table 3).

In a long-term safety study, telcagepant was used by 641 patients for acute migraine attacks for up to 18 months and was generally well tolerated in long-term intermittent treatment [101].

The most worrying part of the CGRP receptor antagonism project has been elevation of transaminases. This was not a problem when administrating telcagepant intermittently for single acute attacks of migraine; however, moving into prophylaxis showed a slightly disturbing picture. According to the NIH clinical trials registry, a Phase IIa randomized, double blind, placebo-controlled, parallel assignment clinical trial (NCT00797667, MK0974–049) assessing telcagepant (140 and 280 mg oral, twice-daily for 12 weeks) for prevention of migraine in otherwise healthy migraineurs was initiated (n = 600 planned). This trial was terminated in April 2009 because some subjects experienced elevated liver enzymes during the last part of the trial. None of these patients fulfilled the criteria of Hy's law (a prognostic indicator that a pure drug-induced liver injury leading to jaundice, without a hepatic transplant, has a case fatality rate of 10–50% [102]). The exposure achieved in this study was much higher than the acute migraine dose due to an accumulation of drug with daily treatment. Similar hepatic signal were not seen with acute intermittent therapy suggesting that the potential for hepatic toxicity may be time and dose dependent.

Comparison of telcagepant with triptans

In one randomized clinical trial, telcagepant 300-mg

Table 2. Efficacy of MK-0974 (telcagepant), placebo, rizatriptan and zolmitriptan in five clinical trials.

Study	Telcagepant tablet 140 mg/capsule 150 mg† (% [n])	Telcagepant tablet 280 mg/capsule 300 mg† (% [n])	Placebo (% [n])	Rizatriptan 10 mg (oral) (% [n])	Zolmitriptan 5 mg (oral) (% [n])	Ref.
Headache free at 2 h						
Ho *et al.* (2008)		45* (38‡)	14 (115‡)	33** (34‡)		[97]
Ho *et al.* (2008)	17*** (331§)	27**** (353§)	10 (343§)		31****¶ (342§)	[100]
Connor *et al.* (2009)	23* (381‡)	24* (371‡)	11 (365‡)			[98]
Ho *et al.* (2010)	22* (556§)	25* (534§)	10 (539§)			[99]
Connor *et al.* (2011)		39 (592§)		48# (294‡)		[101]††
Headache relief at 2 h						
Ho *et al.* (2008)		68** (38‡)	46 (115‡)	70** (34‡)		[97]
Ho *et al.* (2008)	50**** (331§)	55**** (353§)	28 (343§)		56**** (342§)	[100]
Connor *et al.* (2009)	54* (381‡)	56* (371‡)	33 (365‡)			[98]
Ho *et al.* (2010)	59* (556§)	57* (534§)	33 (539§)			[99]
Connor *et al.* (2011)		66 (592§)		71# (294‡)		[101]††
Absence of photophobia at 2 h						
Ho *et al.* (2008)		54 (38‡)	39 (115‡)	53 (34‡)		[97]
Ho *et al.* (2008)	45**** (331§)	51**** (353§)	29 (342§)		50**** (342§)	[100]
Connor *et al.* (2009)	46* (381‡)	48* (371‡)	33 (365‡)			[98]
Ho *et al.* (2010)	52* (554§)	52* (534§)	41 (539§)			[99]
Connor *et al.* (2011)		58 (592§)		63 (294‡)		[101]††
Absence of phonophobia at 2 h						
Ho *et al.* (2008)		70*** (38‡)	43 (115‡)	54 (34‡)		[97]
Ho *et al.* (2008)	54**** (331§)	58**** (353§)	37 (342§)		55**** (340§)	[100]
Connor *et al.* (2009)	50** (381‡)	56* (371‡)	42 (365‡)			[98]
Ho *et al.* (2010)	61* (555§)	59* (534§)	49 (537§)			[99]
Connor *et al.* (2011)		63 (592§)		66 (294‡)		[101]††
Absence of nausea at 2 h						
Ho *et al.* (2008)		78 (38‡)	65 (115‡)	83** (34‡)		[97]
Ho *et al.* (2008)	67*** (330§)	60*** (352§)	55 (342§)		71**** (341§)	[100]
Connor *et al.* (2009)	69* (381‡)	70* (371‡)	54 (365‡)			[98]
Ho *et al.* (2010)	73* (553§)	72* (534§)	63 (538§)			[99]
Connor *et al.* (2011)		76 (592§)		79# (294‡)		[101]††
2–24 h sustained pain freedom						
Ho *et al.* (2008)		40* (38‡)	11 (115‡)	18 (34‡)		[97]
Ho *et al.* (2008)	11*** (328§)	20**** (351§)	5 (343§)		18**** (341§)	[100]
Connor *et al.* (2009)	16* (381‡)	17* (371‡)	7 (365‡)			[98]
Ho *et al.* (2010)	16* (553§)	19* (529§)	6 (537§)			[99]
Connor *et al.* (2011)		34 (592§)		38 (294‡)		[101]††

†300 and 150 mg capsules are bioequivalent to 280 and 140 mg tablets, respectively.
‡Number of treated patients.
§Number of patients in the end point full analysis-set.
¶p < 0.0001 for the telcagepant 150 mg versus zolmitriptan 5 mg pairwise comparison.
#Odds ratio in significant favor of rizatriptan 10 mg over telcagepant 280/300 mg.
††Mean percent of patients' attacks (up to eight/month) with response during an 18-month treatment period.
*p < 0.001 versus placebo; **p < 0.05 versus placebo; ***p < 0.01 versus placebo; ****p < 0.0001 versus placebo.

was equipotent to zolmitriptan 5 mg (Table 2). Based on results from a meta-analysis, rizatriptan 10 mg (41%) and almotriptan (35%) seem superior to telcagepant (26%) for pain freedom at 2 h, whereas rizatriptan 10 mg (25%) showed no difference from telcagepant 300 mg (19%) for sustained pain freedom (2–24 h) [103].

In a *post hoc* analysis, data from the randomized, controlled trial of telcagepant (150, 300 mg) zolmitriptan 5 mg, or placebo for a moderate/severe migraine, responder rates were analyzed according to patients' self-reported historical triptan response [104]. This suggests that different patients may respond to triptans or telcagepant 300 mg.

Compared to triptans, telcagepant appears to have less of the AEs that are commonly associated with triptans (Table 3). In a long-term tolerability study, fewer triptan-related AEs, such as asthenia, chest discomfort, fatigue, myalgia, dizziness, paresthesia and throat tightness, (difference: -6.2%; 95% CI: -10.4, -2.6; $p < 0.001$) and drug-related AEs (difference: -15.6%; 95% CI: -22.2, -9.0) were reported for telcagepant 280/300 mg versus rizatriptan 10 mg. The most common AEs appeared to have generally similar incidence proportions between the treatment groups. Those with an incidence >5% in the telcagepant group were dry mouth (9.7%, rizatriptan = 13.7%), somnolence (9.2%, rizatriptan = 16.6%), dizziness (8.9%, rizatriptan = 10.2%) and nausea (9.0%, rizatriptan = 6.4% [101].

Data from the study MK-0974–011 [100] were used to evaluate new composite efficacy-plus-tolerability end points in a *post hoc* analysis [105]. For the most strict end point, 2–24 h sustained pain freedom and no AEs from 0–24 h (SPF24NAE), telcagepant 300 mg showed superiority over zolmitriptan 5 mg (14.2% [95% CI: 10.8–18.3] vs 8.8% [95% CI: 6.0–12.3]; $p<0.05$), whereas telcagepant 150 mg did not. These results need to be confirmed in an appropriately powered study in which the composite end points are prespecified and multiplicity adequately addressed.

Until recently, telcagepant was considered to have the potential of becoming the first drug of choice (compared with triptans) for patients with migraine and cardiovascular diseases or high risk of cardiovascular diseases. It could also have been a good choice if the migraine patient had intolerable AEs when treating with triptans [106]. As officially communicated by

Table 3. Adverse events of telcagepant within 48 h after intake in the studies MK-0974-011 and MK-0974-016.

AE	Telcagepant 150 mg MK-0974-011 (n = 334; % [n])	Telcagepant 150 mg MK-0974-016 (n = 381; % [n])	Telcagepant 300 mg MK-0974-011 (n = 352; % [n])	Telcagepant 300 mg MK-0974-016 (n = 370; % [n])	Placebo MK-0974-011 (n = 349; % [n])	Placebo MK-0974-016 (n = 366; % [n])
Any	28.4 (95)	30.7 (117)	34.1 (120)	34.6 (128)	30.7 (107)	30.9 (113)
Dry mouth	5.4 (18)	4.5 (17)	6.0 (21)	5.1 (19)	3.7 (13)	5.2 (19)
Somnolence	4.5 (15)	3.7 (14)	5.1 (18)	2.7 (10)	4.0 (14)	3.0 (11)
Dizziness	4.2 (14)	2.4 (9)	5.1 (18)	5.4 (20)	5.7 (20)	3.3 (12)
Nausea	3.9 (13)	3.4 (13)	4.5 (16)	4.6 (17)	3.7 (13)	5.5% (20(
Fatigue	4.2 (14)	3.7 (14)	4.3 (15)	6.5 (24)	2.3 (8)	3.8 (14)
Vomiting	0.6 (2)	0.8 (3)	2.3 (8)	1.6 (6)	0.6 (2)	2.7 (10)
Paresthesia	1.2 (4)	1.3 (5)	1.7 (6)	2.2 (8)	1.4 (5)	2.5 (9)
Epigast pain	ND	1.0 (4)	ND	3.2 (12)	ND	1.6 (6)
Chest discomfort	0.3 (1)	ND	0.9 (3)	ND	0.3 (1)	ND
Asthenia	0	ND	0.9 (3)	ND	0.9 (3)	ND
Headache	ND	0.8 (3)	ND	0.5 (2)	ND	2.2 (8)
Feeling hot	1.8 (6)	ND	0.6 (2)	ND	0.3 (1)	ND
Vertigo	ND	0.5 (2)	ND	1.4 (5)	ND	2.5 (9)
Throat tightness	0	ND	0.3 (1)	ND	0	ND
'Triptan'†	2.1 (7)	ND	4.0 (14)	ND	3.4 (12)	ND

Data are proportion (%) of patients with number of patients with the AE (n) within parenthesis.

†Triptan-related AEs ('Triptan') is a prespecified grouping of chest pain, chest tightness, asthenia, paresthesia, dysesthesia and hyperesthesia. In MK-0974-011, this was reported by 10.4% within 48 h of patients treated with zolmitriptan 5 mg (n = 345).

AE: Adverse event; ND: No data reported.

Data taken from [98,100].

Table 4. Efficacy of MK-3207.

Drug and dose	Headache free at 2 h (% [n])	Headache relief at 2 h (% [n])	Absence of photophobia at 2 h (% [n])	Absence of phonophobia at 2 h (% [n])	Absence of nausea at 2 h (% [n])	2–24 h sustained pain freedom (% [n])
MK-3207 10 mg (oral; n = 63)	25 (16)*	57 (36)**	51 (32)	56 (35)	70 (44)	21 (13)
MK-3207 20 mg (oral; n = 63)	19 (12)	57 (36)**	43 (27)	56 (35)	67 (42)	16 (10)
MK-3207 50 mg (oral; n = 65)	22 (14)	63 (41)***	49 (32)	58 (38)*	68 (44)	18 (12)
MK-3207 100 mg (oral; n = 59)	24 (14)*	52 (31)*	44 (26)	52 (31)	70 (41)	20 (12)
MK-3207 200 mg (oral; n = 58)	36 (21)***	69 (40)***	57 (33)*	64 (37)**	78 (45)**	30 (17)**
Placebo (n = 133)	10 (13)	36 (48)	38 (51)	43 (57)	59 (79)	8 (10)

Data are proportion (%) of patients with number of patients fulfilling end point (n) within parenthesis.

*p <0.05; **p < 0.01; ***p < 0.001 for the active versus placebo comparison.

Data taken from [107].

MSD on 29 July 2011, the telcagepant program was, however, discontinued.

■ Other CGRP receptor antagonists investigated in clinical trials

Merck also advanced a second oral CGRP receptor antagonist, MK-3207, to clinical trials because it showed a better oral bioavailability and was a more potent drug (Table 4) [86,107]. However, in clinical testing it was found to induce liver enzyme elevations after a few doses; development of MK-3207 was, therefore, discontinued. It is believed by some researchers that hepatotoxicity may be a class effect demonstrated by the discontinuation of development of both MK-3207 and telcagepant. Future developments on CGRP receptor antagonists will prove this right or wrong.

The initial absorption of BI 44370 TA, another oral CGRP receptor antagonist, is delayed and reduced during migraine attacks, but overall absorption is not meaningfully affected [108]. In a recently published Phase II trial, efficacy of the drug in acute migraine attacks was shown in a dose-dependent manner [109]. The primary end point, pain-free after 2 h, was reached by significantly more subjects in the BI 44370 TA 400 mg (20/73 = 27.4%) and eletriptan 40 mg (24/69 = 34.8%) groups compared with placebo (6/70 = 8.6%, $p = .0016$), but not by subjects in the BI 44370 TA 200-mg group (14/65 = 21.5%; Table 5). The effect of BI 44370 TA 50 mg (5/64 = 7.8%) was similar to that of placebo. Analysis of secondary end points supported the conclusion from the primary analysis. The frequency of AEs was low in all groups. Increased liver function tests were found in one subject. Detailed review of the subject's medical status showed concomitant medications and diseases as well as alcohol consumption. It is, therefore, difficult to draw a conclusion. The beneficial effect of BI 44370 TA has to be replicated in a large Phase III trial.

Very recently, Bristol-Myers Squibb registered the protocols of two clinical trials examining a new entry gepant, BMS-927711 [201]. The first (Phase I, ID Number CN170–004) is an open-label study to evaluate the PK of BMS-927711 in patients with migraine during and between attacks. Participants will be randomized to oral doses of BMS-927711 300 mg or 600 mg, and plasma concentrations of the drug will be measured over time. The study primary completion date is set to March 2012. The second study (Phase IIb, ID Number CN170–003) is a double-blind, randomized, placebo controlled dose-ranging trial for the acute treatment of migraine. Oral doses of BMS-927711 10, 25, 75, 150, 300 and 600 mg will be compared with placebo and a dose of BMS-927711 100 mg will be compared with sumatriptan. The estimated final collection date for the primary outcome measure (pain freedom 2 h postdose) is in June 2012.

Where do the gepants act in migraine?

Although it has been demonstrated that CGRP receptor antagonism is an effective way to abort acute migraine attacks and treat migraine-associated symptoms, questions remain as to how CGRP receptor antagonists work. Provided the gepants have access to the receptor sites in the CNS or in the periphery, including vasculature, they are potent and selective inhibitors of CGRP receptors in man.

Another argument is the apparently very high dose of CGRP antagonists and triptans needed to treat a migraine attack. The limited passage over the BBB of not only triptans, but also CGRP antagonists may be due to high protein binding, low inherent passage through the BBB and being substrate for the efflux trough system P-glycoprotein pump. The CGRP antagonists, olcegepant and telcagepant, are very potent drugs [77] with an IC_{50} of 0.1 and 10 nM, respectively,

Table 5. Efficacy of BI 44370, eletriptan and placebo.

Drug and dose	Headache free at 2 h (% [n])	Headache relief at 2 h (% [n])	Absence of photophobia at 2 h (% [n])	Absence of phonophobia at 2 h (% [n])	Absence of nausea at 2 h (% [n])	2–24 h sustained pain freedom (% [n])
BI 44370 50 mg (oral; n=64)	8 (5)	31 (20)	39 (25)	42 (27)	61 (39)	5 (3)
BI 44370 200 mg (oral; n=65)	22 (14)	51 (33)*	46 (30)	54 (35)	58 (38)	20 (13)
BI 44370 400 mg (oral; n=73)	27 (20)**	56 (41)*	56 (41)**	63 (46)***	70 (51)**	20 (15)*
Placebo (n=70)	9 (6)	19 (13)	33 (23)	41 (29)	46 (32)	7 (5)
Eletriptan 40 mg (oral; n=69)	35 (24)*	56 (39)*	64 (44)*	64 (44)***	65 (45)***	22 (15)***

*p < 0.0005; **p < 0.005 ***; p < 0.025 for the active versus placebo comparison.
Data are proportion (%) of patients with number of patients fulfilling end point (n) within parenthesis.
Data taken from [109].

on human brain and MMA. The plasma concentration after olcegepant 2 mg iv. is approximately 200 nM and for 300 mg telcagepant it is approximately 4 µm. There is, therefore, a huge difference between the low concentration of olcegepant and telcagepant needed for CGRP blockade of human cranial arteries and the concentration needed for an effect in migraine.

Another argument for a central site of action of CGRP antagonists was found in cats where the CGRP antagonist BIBN4096BS (olcegepant) inhibited the stimulation-induced neuronal firing in the brainstem [110]. The data suggested that there are central CGRP receptors in the trigeminocervical complex that can be inhibited by CGRP receptor blockade. Here the ED_{50} of olcegepant used was 31 µg/kg [18], which is roughly equivalent to 2 mg iv. in man.

Given the high potency of olcegepant and telcagepant, it was initially anticipated that a relatively low dose of telcagepant would likely be efficacious by blocking peripheral CGRP receptors. Indeed, in a capsaicin-induced vasodilatation study, it was shown that the EC_{90} to block peripheral CGRP receptor-mediated vasodilatation was determined to be at 300 or 900 nM [111]. The relatively flat concentration–response curve above 900 nM indicates that at or above this plasma concentration, telcagepant is maximally blocking the peripheral CGRP receptor in humans. Thus, it was surprising that relatively high doses of telcagepant (150 and 300 mg) were needed to achieve antimigraine efficacy [98,99]. At these doses, the mean plasma concentrations are approximately two- to four-fold higher than 900 nM, suggesting that larger doses than those producing maximal peripheral CGRP receptor inhibition are necessary for antimigraine efficacy. Similarly, this dose is also three orders of magnitude higher than the pA_2 of telcagepant in inhibiting αCGRP-induced vasodilatation in human cerebral and coronary arteries *in vitro* (8.0 to 8.3, which represents ~1 and 10 nM).

Can telcagepant work centrally, given that it is a PGP substrate? The *in vivo* CSF level of telcagepant was evaluated in cisterna magna-ported Rhesus monkeys as a surrogate to the clinical experience. PK parameters were determined in CSF and plasma following oral dosing. A CSF/plasma ratio (%) was computed as an index of CNS penetrability. The CSF/plasma ratio is approximately 1.4% (C_{max} = 8.7 nM plasma and 127 nM CSF), suggesting that telcagepant has some brain penetration potential. At this penetration, the telcagepant CSF level could be as high as 60 nM, which is above the K_i (0.77 nM) and IC_{50} (2.2 nM) of telcagepant. Thus, at clinical doses, based on data from rhesus CSF study, telcagepant could potentially achieve a relevant CSF concentration [112]. Nevertheless, one must interpret these data with caution as CSF levels should not be equated as receptor occupancy. If we follow this reasoning, a concentration of drug equal to the pA_2 value may not be sufficient to decrease a functional response since it only shifts the concentration response curve twofold to the right. Chan *et al.* [82] advocated that a concentration of at least ten-times pA_2 would be needed to functionally inhibit the relaxations to CGRP. This is actually what we may obtain in the CSF.

Similarly, the CGRP blocker olcegepant also has poor penetration across the BBB, and cannot be used as an oral drug because of its dipeptide structure. While systemic olcegepant effectively blocks the CGRP-induced temporal artery dilatation it does not modify the tone of cerebral vessels [85]. In agreement with this observation perfusion studies on the isolated MCA revealed that luminal olcegepant did not block abluminal CGRP-induced vasodilatation [67]; similar observations have been seen for telcagepant [Edvinsson L, Unpublished Data]. However, if olcegepant is given by local microiontophoresis, it is a potent inhibitor of activated trigeminocervical neurons *in vivo* (a way to circumvent the BBB) [110] or given systemically in very high doses [113]. These studies demonstrate the presence of functional CGRP receptors on the second-order trigeminal neurons. Furthermore, an *in vivo* C_{max} of >200 nM is necessary to show clinical efficacy [92]. Since the K_i of olcegepant is in the 0.1 nM range (revealing a difference in inhibition concentration of >2000), it shows the need to use a high dose of the antagonist to act on receptors in part protected by the BBB and thus effectively rules out the neurogenic inflammation theory in the meningeal circulation as the prime target for the antimigraine effect of the CGRP receptor blockers [67]. The lack of sensitization of meningeal nociceptors by topical CGRP in rats might further indicate a nonvascular involvement of CGRP in migraine [22]. It should, however, be pointed out that the CGRP receptor blockers do act at meningeal receptors as part of their therapeutic action.

Why are such high doses required for acute migraine efficacy? It could be the case that in a migraine population, higher doses are needed to maximally inhibit the peripheral CGRP receptor in a majority of the patients. However, studies of migraine and healthy volunteers have not revealed a difference between the two groups in sensitivity to CGRP or nitric oxide [114]. Another possibility is that peripheral CGRP receptor inhibition may not be sufficient for antimigraine efficacy and that central engagement may also be required. Given the widespread distribution of CGRP receptor in several migraine-relevant brain areas such as hypothalamus (autonomic function), cerebellum (inhibition of brainstem centers), periaqueductal gray (modulation of pain), superior and inferior colliculi (phono- and photophobia) in addition to the trigeminal complex, there are many potential ways that CGRP antagonism may abort or modify acute migraine attacks.

The role of CGRP in the brain is not described in detail but compared with other neuromodulator neuropeptides. CGRP is often coexpressed with other neurotransmitters, such as intermedin, AM, neuropeptide Y and dopamine. It may co-operate with Y1 and Y2 receptors, PPARγ receptor on allodynia, dopamine receptors and vanilloid receptor-1 [9,40]. However, it is still unclear how CGRP and CGRP receptors interact with these receptors and mediator molecules. In addition, CGRP has been shown to modulate the cholinergic system by antagonizing neuronal nicotinic acetylcholine receptor (nAChR) in the autonomic nervous system. Through this action, CGRP may inhibit background synaptic noise at cholinergic synapses, thus contributing to the fine-tuning of nicotinic synaptic transmission [115]. CGRP has been shown to be able to modulate pain transmission by increasing the discharge frequency of wide dynamic neurons in the dorsal horn and thus facilitate the transmission of nociceptive signals [116]. The CGRP receptor antagonist CGRP8–37 reduces mechanical allodynia and hyperalgesia in rats [117], which supports a role for CGRP in this form of trigeminal plasticity.

Finally, CGRP may modulate neuronal function through interaction with glial CGRP receptors [118]. It is thought that CGRP is secreted by neurons and then activates the surrounding glial cells, which in turn can activate many pro-nociceptive mediators. The neurons in the TG are surrounded by a network of satellite glial cells, which contains CLR/RAMP1 [71]. CGRP differentially regulates gene and protein expression in TG cells [119]. Culture of TG causes upregulation and enhanced expression of CGRP via the ERK1/2 pathway [120]. In addition it also causes activation of the different cells in the TG with enhanced expression of cytokines and MAPKs [121]. Exogenous CGRP was found to induce expression of some cytokines, putatively in the satellite glial cells via MAPK activation. The modulating effect of CGRP on glial function is not only limited to trigeminal ganglia, but has also been demonstrated in other brain areas such as cerebellum [122] and neuromuscular junctions [123].

One area that may be of particular interest is the high expression of CGRP and CGRP receptors in the cerebellum [124]. The cerebellum is known to be important in modulating many cortical motor and sensory inputs. Subtle clinical cerebellar alterations have been found in migraine [125]. Moreover, it is known that cerebellum exerts an inhibitory control on cerebral cortex and abnormalities in visual and motor cortex excitability consistent with a lack of inhibitory efficiency have been described in migraine. In a study by Brighina *et al.*, cerebellar conditioning transcranial magnetic stimulation showed a significant deficit of cerebellar inhibition in migraine patients as compared with controls [126], suggesting that migraine patient may have a deficit in filtering sensory inputs. The deficit in filtering somatosensory, visual and auditory inputs may lead to head pain, photophobia and phonophobia respectively. Recent detailed immunohistochemistry revealed that there is a rich and exclusive expression of CGRP in the Purkinje cell

bodies while the CGRP receptor elements are found on the surface of the Purkinje cell bodies and in the fibers throughout the cerebellum. However, the glial cells that tightly surround them were without these [124]. CGRP receptors were also located in inhibitory interneurons: CGRP may elicit calcium responses of cultured astrocytes and Bergman glial cells [127]. Furthermore, CGRP may suppress both the spontaneous firing rate neuron–glial of olivary neurons, as well as the enhanced activity-induced by application of excitatory amino acids [16]. These findings suggest that CGRP may be involveed in neuron–glial interactions influencing neuronal activity and may play an important role in cerebellum's ability to modulate sensory inputs.

Although CGRP has been shown to facilitate nociceptive transmission through neuromodulation in some parts of the brain, it may be antinociceptive. For example, intracerebroventricular injection of CGRP produced an antinociceptive effect in rats and mice [128]. CGRP produced significant antinociceptive effects in the nucleus raphe magnus of rats, an action that appeared to involve opioid receptors [129]. Although these observations could reflect a physiological action of CGRP, the doses that were used in these studies were quite high, raising the possibility that desensitization and internalization of CGRP receptors led to reduced responsiveness to CGRP.

Conclusion

It appears clear that available CGRP receptor antagonists tested so far are effective in migraine [130]. The rationale for the further development of specific CGRP antagonists, firmly based on the available translational research, is now regarded as a prime target for the development of novel antimigraine therapies. There is an excellent correlation between CGRP release and pain in migraine headache, which points towards the potential usefulness of a specific CGRP antagonist in the treatment of primary headaches [22]. The demonstration that triptans have the ability to inhibit the release of CGRP supports this view, but triptans suffer from significant cardiovascular side-effects [131]. The progress in the demonstration of the unique molecular biology and functional organization of the CGRP family of receptors provide understanding of the elements of the CGRP receptor function. The development of small molecules with selectivity for human CGRP receptors has opened up the possibility to examine this in the clinical situation. The clinical trials with olcegepant and telcagepant in man have provided some answers; CGRP antagonism is an effective principle and has no significant acute side effects. At present there is no evidence that the novel CGRP receptor antagonists have direct contractile effects [77–80,132,133], and this may provide a significant advantage over the triptans. The outstanding question is to understand the contribution between peripheral and central CGRP biology to migraine pathophysiology. Future research and development of PET ligands may shed some light and further help our understanding of migraine pathophysiology.

Executive summary

Background
- Migraine is a frequent disorder worldwide (13% of adults) that is receiving much attention. The pain is related to the trigeminovascular system.

Basic facts on CGRP
- CGRP is widely expressed in the CNS and PNS, and is particularly related to the sensory nerves. CGRP is a potent vasodilator and released in conjunction with migraine attacks.

CGRP receptors
- The CGRP receptor is a G-protein-coupled receptor of the B-type. It consists of the two proteins calcitonin-like receptor and RAMP1, and couples to RCP and adenylyl cyclase for cellular activation.

CGRP receptor antagonism
- There exists a new family of CGRP receptor antagonists, the gepants. Olcegepant and telcagepant have been studied and characterized as very potent CGRP receptor blockers.

Clinical studies on CGRP receptor antagonists for migraine
- The ability of CGRP receptor antagonists to treat acute migraine attacks has been established in clinical trials. Adverse events reported by patients have been similar to placebo. The most worrying part of the CGRP receptor antagonism project has been elevation of liver transaminases.

Where do the gepants act in migraine?
- The gepants have been shown to block CGRP responses in cranial arteries. They are hypothesized to also have effects on different parts of the trigeminal system and in migraine-related regions in the CNS.

Conclusion
- The gepants are now an established and well defined group of CGRP blockers. They are proven to have good antimigraine effects in clinical trials with low degrees of side-effects.

Future perspective

We anticipate that ongoing research will increase our knowledge regarding the localization and function of CGRP and its receptors in humans. As pointed out in this review there are now at least three major drug companies with strong interest in migraine and the entry of a clinical program from BMS offers future hope that this form of migraine therapy will soon reach the patients.

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